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# AN EFFICIENT SYNTHESIS OF 4-HYDROXY-1*H*-INDOLE-2-CARBONITRILE AND ITS CONVERSION TO DPI 201-106

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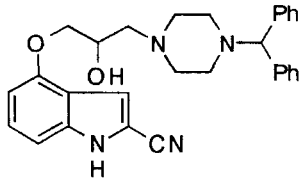
A three-step synthesis of 4-hydroxy-1*H*-indole-2-carbonitrile (**3**) from commercially available 1,5,6,7-tetrahydro-4*H*-indol-4-one (**4**) via cyanation and subsequent halogenation/ dehydrohalogenation proceeds in 84% overall yield. The conversion of **3** into positive inotrope DPI 201-106 (**1**) is also described.

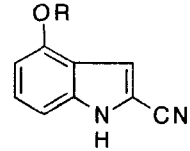


DPI 201-106 **1** is a novel antiarrhythmic agent which prolongs refractoriness by delaying the inactivation of cardiac sodium channels.[1] As part of our cardiovascular discovery program, a supply of DPI was required for use as a reference standard.

The synthesis of DPI as reported in the literature appears to be straightforward,[2] the key intermediates being 4-hydroxy-2-cyano-1*H*-indole **3** and its glycidyl ether **2**. Compounds **2** and **3** are versatile intermediates, and can be




**1** DPI 201-106




**2** R=2,3-epoxypropyl
**3** R=H

used in the synthesis of a number of biologically active molecules such as cyanopindolol[3] and BDF 9148,[4] and in the synthesis of a variety of tools used to explore β-adrenergic[5] and 5-HT receptors.[6] The source of cyanoindole derived compounds used in these biological experiments is almost exclusively referenced as a gift from Sandoz, the manufacturer of DPI 201-106, and the patents describing these materials contain few experimental details.[2] In 1987 Pitha and coworkers reported difficulty in preparing **2**, and outlined a synthesis of **2** (via **3**) with an abbreviated experimental procedure.[7] This route to **3** proved poorly reproducible in our hands, and recently others have reported a similar experience.[8]

Frustrated by the difficulty in performing what appeared to be straightforward functional group manipulations, attention was turned to developing an alternative synthesis of cyanoindole **3**. Herein is reported an efficient 3-step synthesis which can afford **3** in large quantities and in high yield.

The key to this alternative route is the introduction of the nitrile group directly onto an intact indole ring precursor, which subsequently can be transformed into the desired 4-hydroxyindole. Thus, commercially available 1,5,6,7-tetrahydro-4*H*-indol-4-one **4**[9] was treated sequentially with chlorosulfonylisocyanate[10] and DMF at -20°C to afford the carbonitrile **5** in 89% yield (Scheme). Using a method described by Matsumoto,[11] **5** was brominated with copper (II) bromide to give **6** (96%), which was then dehydrohalogenated without purification to afford the desired hydroxyindole **3** of high purity and in excellent yield. In contrast to the examples cited by Matsumoto, *N*-protection of the indole was not necessary.

With this critical intermediate in hand, efforts were next directed toward its conversion to DPI 201-106 via the epoxide **2**. Once again, difficulty was encountered in synthesizing **2** from **3** using the method reported by Pitha.[7] In our

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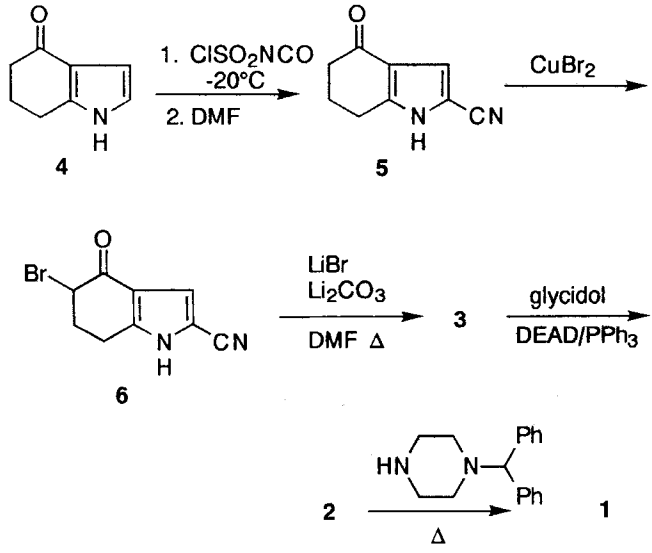


hands, Pitha's conditions (10 molar excess epichlorohydrin, catalytic morpholine, reflux 2.5 h) afforded a mixture of O-alkylated, N-alkylated, and O,N-bis-alkylated indole products in poor yield. However, the coupling of **3** with glycidol under Mitsunobu conditions afforded an adequate yield of epoxide **2** (53% based on 26% recovered **3**), which was readily converted to DPI 201-106 by thermolysis with benzhydrylpiperazine.[2c] This glycidol coupling procedure offers the additional advantage in that it is readily amenable to the synthesis of a single enantiomer of DPI 201-106, as both optical isomers of glycidol are commercially available.[12] Since only one equivalent of glycidol is required, it is possible to obtain (*R*)- or (*S*)-DPI 201-106 without wasting a large excess of a costly chiral synthon.

In summary, an easy, reliable synthesis of **3** has been achieved. This efficient 3-step procedure avoids the use of potentially unstable azide

intermediates,[8] and affords the 4-hydroxy-1*H*-indole-2-carbonitrile product in 84% overall yield from commercially available starting materials. The subsequent transformation of **3** to DPI 201-106 through the epoxide **2** is one example of the use of this valuable intermediate.

## Experimental

General Methods. Nuclear magnetic resonance spectra were obtained at 300 MHz and are reported in ppm (δ units) downfield of internal trimethylsilane. Infrared spectra were obtained as 1% KBr pellets. Mass spectra were determined under methane chemical ionization conditions. Melting points were determined in open capillary tubes and are uncorrected. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. Organic layers were dried over $MgSO_4$, and concentrated in vacuo with a Buchi rotary evaporator. Column chromatography was performed with 230-400 mesh silica gel 60 (EM Science). THF was distilled from sodium/benzophenone ketyl prior to use. All other chemicals were obtained from commercial suppliers and were used as received.

**2-Cyano-1,5,6,7-tetrahydro-4*H*-indol-4-one (5).** To a solution of 1,5,6,7-tetrahydro-4*H*-indole-4-one **4** (10.3 g, 76.3 mmol) in acetonitrile (1.00 L) at -20°C was added chlorosulfonylisocyanate (32.4 g, 229 mmol) over 10 min, and the reaction was allowed to stir at -20°C for 45 min. DMF (60.0 ml) was added over 20 min as the temperature was maintained at -20°C. The reaction was placed in an ice bath and was stirred at 0°C for 30 min. Aqueous sodium carbonate solution (150 ml) was added, the layers were separated, and the organic phase was concentrated to an aqueous suspension. The light brown solids were collected, washed with water, and dried in a vacuum oven (25 torr) at 70°C to afford 6.61 g of crude **5**. The aqueous phase and washings were combined and brought to pH 3,

saturated with NaCl, and extracted with ethyl acetate (3 x 100 ml). The organic extracts were dried and concentrated to afford another 4.65 g of **5** as a crude brown solid. The crude products were combined and recrystallized from ethyl acetate to yield 9.33 g of pure **5**, mp 239-240°C. The mother liquor was chromatographed with 50% ethyl acetate-hexanes to afford an additional 1.55 g product, bringing the total yield to 10.88 g (89%). $^1$H NMR (DMSO-$d_6$) δ 12.68 (br s, 1H), 7.13 (s, 1H), 2.77 (dd, $J_1$=6.2 Hz, $J_2$=6.2 Hz, 2H), 2.35 (dd, $J_1$=6.7 Hz, $J_2$=6.0 Hz, 2H), 2.00 (m, 2H); IR 3172, 3124, 3058, 2940, 2222, 1650, 1500 cm$^{-1}$; MS (CI) *m/z* 161 ($MH^+$). Anal. calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.31; H, 4.95; N, 17.46.

**5-Bromo-2-cyano-1,5,6,7-tetrahydro-4*H*-indol-4-one (6).** A suspension of **5** (7.50 g, 46.9 mmol) and copper (II) bromide (22.0 g, 98.4 mmol) in ethyl acetate (140 ml) was heated at reflux for 2.5 h. After cooling to room temperature, the mixture was filtered through Celite, washing with ethyl acetate. The filtrate was extracted with 100 ml sodium bicarbonate solution, dried, and concentrated to afford 10.8 g (96% recovery) of **6** as a gray solid which was used without further purification in the subsequent transformation. An analytical sample was recrystallized from methanol, mp 201°C (dec); $^1$H NMR (DMSO-$d_6$) δ 12.91 (br s, 1H), 7.25 (s, 1H), 4.77 (dd, $J_1$=3.6 Hz, $J_2$=3.6 Hz, 1H), 2.85 (m, 2H), 2.52 (m, 1H), 2.35 (m, 1H); IR 3172, 3104, 2941, 2225, 1656, 1502 cm$^{-1}$; MS (CI) *m/z* 239 ($MH^+$). Anal. calcd for $C_9H_7N_2BrO$: C, 45.22; H, 2.95; N, 11.72. Found: C, 44.83; H, 2.80; N, 11.50.

**4-Hydroxy-1*H*-indole-2-carbonitrile (3)** To a solution of crude **6** (9.81 g, 41.0 mmol) in DMF (410 ml) were added lithium carbonate (3.34 g, 45.2 mmol) and lithium bromide (3.92 g, 45.2 mmol) sequentially, and the resulting mixture was heated at reflux for 1h. The solvent was then removed in vacuo, and the

resulting black tarry residue was chromatographed directly, eluting with 2% methanol-chloroform to afford 6.44 g (99%) of **3** as a purple-brown solid. NMR analysis of this product revealed no impurities. An analytical sample was obtained as white needles from methanol-chloroform, mp 193-194°C (lit. mp[7], 188-190°C); $^1$H NMR (DMSO-$d_6$) δ 12.14 (br, 1H), 9.89 (s, 1H), 7.30 (s, 1H), 7.09 (dd, $J_1$=8 Hz, $J_2$=8 Hz, 1H), 6.84 (d, J=8 Hz, 1H), 6.43 (d, J=8Hz, 1H); IR 3368, 3276, 2231, 1629, 1587, 1515 cm$^{-1}$; MS (CI) *m/z* 159 ($MH^+$). Anal. calcd for $C_9H_6N_2O$: C, 68.35; H, 3.82; N, 17.71. Found: C, 68.15; H, 3.71; N, 17.66.

**Conversion of 3 into DPI 201-106 (1)** A solution of DEAD (380 mg, 2.18 mmol) in THF (3 ml) was added dropwise to a mixture of **3** (300 mg, 1.90 mmol), glycidol (141 mg, 1.90 mmol), and triphenylphosphine (548 mg, 2.09 mmol) in THF (19 ml) at 0°C. The reaction was allowed to warm to room temperature over 1h, and was subsequently stirred at room temperature for 6h. The solvent was then removed in vacuo, and the purple residue was chromatographed, eluting with 20% ethyl acetate-hexanes to afford 237 mg of a product which was determined by NMR to be a 3:2 mixture of **2** and **3** (53% based on 26% recovered **3**). This material was dissolved in acetone, and 187 mg (0.743 mmol) of benzhydrylpiperazine was added. The solvent was removed in vacuo, and the resulting white foam was then heated in an oil bath at 80°C for 15 min, after which time NMR analysis revealed a clean mixture of **1** and recovered **3**. The crude melt was dissolved in a minimal amount of ethanol and treated with methanesulfonic acid (97.7 mg, 1.01 mmol). Ether was then added to precipitate the crude salt (93% mass recovery), which was collected and recrystallized from ethanol to afford 247 mg (57%; 30% overall from **3**) of the methanesulfonate salt monohydrate of **1** as a white solid, mp 210-213°C. **2**: $^1$H NMR (acetone-$d_6$) δ 7.30 (s, 1H), 7.24 (dd, $J_1$=7.3 Hz, $J_2$=7.3 Hz, 1H), 7.08 (d, J=7.3 Hz, 1H), 6.60 (d, J=7.3 Hz, 1H), 4.44 (dd, $J_1$=11 Hz, $J_2$=3.1

Hz, 1H), 4.00 (dd, $J_1$=11 Hz, $J_2$=6.1 Hz, 1H), 3.38 (m, 1H), 2.86 (dd, $J_1$=5.5 Hz, $J_2$=5.5 Hz, 1H), 2.77 (dd, $J_1$=5.5 Hz, $J_2$=2.5 Hz, 1H).

**1**: $^1$H NMR (DMSO-$d_6$) δ 12.39 (br s, 1H), 9.45 (br s, 1H), 7.45 (m, 5H), 7.30 (m, 4H), 7.25 (m, 3H), 7.03 (d, J=8.3 Hz, 1H), 6.58 (d, J=7.7 Hz, 1H), 5.95 (br s, 1H), 4.44 (s, 1H), 4.33 (m, 1H), 4.05 (m, 2H), 3.6-3.15 (m, 6H), 2.81 (m, 2H), 2.38 (m, 2H), 2.31 (s, 3H); IR 3181, 3003, 2931, 2216, 1620, 1587 cm$^{-1}$; MS (CI) *m/z* 466 (free base $M^+$). Anal. calcd for $C_{29}H_{30}N_4O_2 \cdot CH_3SO_3H \cdot H_2O$: C, 62.05; H, 6.25; N, 9.65. Found: C, 62.02; H, 6.22; N, 9.38.

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